Benefit and Harm of Adding Epinephrine to a Local Anesthetic for Neuraxial and Locoregional Anesthesia

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Abstract: BACKGROUND: This systematic review examines the benefit and harm of adding epinephrine to local anesthetics for epidural, intrathecal, or locoregional anesthesia. METHODS: We searched electronic databases to October 2017 for randomized trials comparing any local anesthetic regimen combined with epinephrine, with the same local anesthetic regimen without epinephrine, reporting on duration of analgesia, time to 2 segments regression, or any adverse effects. Trial quality was assessed using the Cochrane risk of bias tool and a random-effects model was used. Trial sequential analyses (TSA) were applied to identify the information size (IS; number of patients needed to reach a definite conclusion) and were set to detect an increase or decrease of effect of 30%-50%, depending on the end point considered. Alpha levels were adjusted (1%) for multiple outcome testing. RESULTS: We identified 70 trials (3644 patients, 17 countries, from 1970 to 2017). Median number of patients per trial was 44 (range, 9-174). Thirty-seven trials (1781 patients) tested epinephrine for epidural, 27 (1660) for intrathecal, and 6 (203) for locoregional anesthesia (sciatic, femoral, popliteal, axillary blocks). TSA enabled us to conclude that adding epinephrine to epidural local anesthetics could not decrease postoperative pain intensity by 30%, and did not impact the risk of intraoperative arterial hypotension. IS was insufficient to conclude on the impact of epinephrine on the risk of motor block (IS, 4%), arterial hypotension (20%), urinary retention (23%), or pain intensity at rest (27%) during labor. TSA confirmed that adding epinephrine to intrathecal local anesthetics increased the duration of motor block (weighted mean difference [WMD] 64 minutes; 99% CI, 37-91), analgesia (WMD 34 minutes; 99% CI, 6-62), and the time to 2 segments regression (WMD 20 minutes; 99% CI, 11-28). IS was insufficient to conclude on its impact on arterial hypotension (IS, 15%), or when administrated in a combined spinal-epidural, on motor block (IS, 11%) or arterial hypotension (IS, 11%). Adding epinephrine to local anesthetics for a locoregional block increased the duration of analgesia (WMD 66 minutes; 98% CI, 32-100]). CONCLUSIONS: Adding epinephrine to intrathecal or locoregional local anesthetics prolongs analgesia and motor block by no more than 60 minutes. The impact of adding epinephrine to epidural local anesthetics or to a combined spinal-epidural remains uncertain.

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Benefit and Harm of Adding Epinephrine to a Local Anesthetic for Neuraxial and Locoregional Anesthesia: A Meta-analysis of Randomized Controlled Trials With Trial Sequential Analyses

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BACKGROUND: This systematic review examines the benefit and harm of adding epinephrine to local anesthetics for epidural, intrathecal, or locoregional anesthesia.

METHODS: We searched electronic databases to October 2017 for randomized trials comparing any local anesthetic regimen combined with epinephrine, with the same local anesthetic regimen without epinephrine, reporting on duration of analgesia, time to 2 segments regression, or any adverse effects. Trial quality was assessed using the Cochrane risk of bias tool and a random-effects model was used. Trial sequential analyses (TSA) were applied to identify the information size (IS; number of patients needed to reach a definite conclusion) and were set to detect an increase or decrease of effect of 30%–50%, depending on the end point considered. Alpha levels were adjusted (1%) for multiple outcome testing.

RESULTS: We identified 70 trials (3644 patients, 17 countries, from 1970 to 2017). Median number of patients per trial was 44 (range, 9–174). Thirty-seven trials (1781 patients) tested epinephrine for epidural, 27 (1660) for intrathecal, and 6 (203) for locoregional anesthesia (sciatic, femoral, popliteal, axillary blocks). TSA enabled us to conclude that adding epinephrine to epidural local anesthetics could not decrease postoperative pain intensity by 30%, and did not impact the risk of intraoperative arterial hypotension. IS was insufficient to conclude on the impact of epinephrine on the risk of motor block (IS, 4%), arterial hypotension (20%), urinary retention (23%), or pain intensity at rest (27%) during labor. TSA confirmed that adding epinephrine to intrathecal local anesthetics increased the duration of motor block (weighted mean difference [WMD] 64 minutes; 99% CI, 37–91), analgesia (WMD 34 minutes; 99% CI, 6–62), and the time to 2 segments regression (WMD 20 minutes; 99% CI, 11–28). IS was insufficient to conclude on its impact on arterial hypotension (IS, 15%), or when administrated in a combined spinal-epidural, on motor block (IS, 11%) or arterial hypotension (IS, 11%). Adding epinephrine to local anesthetics for a locoregional block increased the duration of analgesia (WMD 66 minutes; 98% CI, 32–100]).

CONCLUSIONS: Adding epinephrine to intrathecal or locoregional local anesthetics prolongs analgesia and motor block by no more than 60 minutes. The impact of adding epinephrine to epidural local anesthetics or to a combined spinal-epidural remains uncertain. (Anesth Analg 2018;127:228–39)

KEY POINTS

- **Question:** What are the benefits and harms of adding epinephrine to local anesthetics for epidural, intrathecal, or locoregional anesthesia?
- **Findings:** Evidence exists that adding epinephrine to intrathecal or locoregional local anesthetics prolongs analgesia and motor block by no more than 60 minutes. Available evidence is insufficient to conclude on other outcomes in these settings, or that adding epinephrine to epidural local anesthetics has any impact at all.
- **Meaning:** Further studies are required to clarify the potential impact of adding epinephrine to epidural local anesthetics and to establish dose-responsiveness of epinephrine when added to local anesthetics for epidural, intrathecal, or locoregional anesthesia.

Neuraxial and locoregional anesthesia are considered techniques of choice for multiple procedures,[1–4] and are frequently chosen as an alternative to general anesthesia. In this context, diverse adjuvants are often administrated in conjunction with local anesthetics (LAs). The adjunction of epinephrine to LAs is widely used for

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Protocol registration: International prospective register of systematic reviews (PROSPERO) (CRD: 42015026148).

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these regional techniques and is thought to prolong anesthesia via a vasoconstrictive effect delaying LA clearance from the injection site,[5,6] and via α_2-adrenoreceptors located in the spinal cord dorsal horn.[7]

The benefits and the incidence of adverse effects associated with the use of epinephrine are not clearly defined. A systematic review of randomized controlled trials (RCTs) investigating epidural epinephrine in various settings, but excluding labor, did not include sufficient data to reach valid conclusions.[8] Intrathecal epinephrine was studied in a meta-analysis that included trials that tested epinephrine added to LAs or to opioids, making the results difficult to interpret.[9]

In the present analysis, we assessed the impact of adding epinephrine to a LA for epidural, intrathecal, or locoregional anesthesia. Any perineural or plexus LA administration was classified as locoregional anesthesia. We aimed to check whether adding epinephrine resulted in any clinically relevant beneficial or harmful effect. Moreover, we aimed to identify, using trial sequential analysis (TSA), whether additional trials, in these different settings, were still needed.

METHODS

Protocol and Registration

The protocol of this meta-analysis was registered in PROSPERO (CRD: 42015026148). Changes to the protocol are notified in the section "Data items." We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations for data reporting.[10]

Inclusion Criteria

We included RCTs comparing any regimen of any LA with epinephrine (experimental intervention) with the same LA regimen but without epinephrine (control intervention). Trials were considered if they tested perineural or plexus blocks, or intrathecal or epidural anesthesia in adults (≥18 years) undergoing any surgery, or in parturients during labor. When an additional adjuvant to the LA was used (eg, opioids or clonidine), the trial was included as long as the adjuvant was used in a strictly controlled manner (ie, administration of the same regimen of the adjuvant in both experimental and control groups). For eligibility, a study had to report on at least one of the following outcomes: duration of analgesia (defined as the time in minutes from injection to first request of analgesia), time from injection to 2 segments regression (for intrathecal anesthesia), need for supplementary LA or systemic rescue analgesia, or incidence of any adverse effects.

Noninclusion Criteria

We did not consider trials reporting on digital nerve blocks, blocks for dentistry, LA infiltration (for instance, subcutaneously) or if epinephrine was added to a regional anesthesia regimen in the absence of an LA. Furthermore, we did not consider studies published as abstracts only.

Information Sources and Searches

Databases (MEDLINE, CENTRAL, EMBASE, GOOGLE SCHOLAR) were searched using a high-sensitivity and low-specificity search strategy. The key words "epidural," "peridural," "extradural," "spinal," "intrathecal," "block," "epinephrine," "adrenaline," "analgesia," and "anesthesia" were combined using the Boolean meanings of "AND" and "OR." The last electronic search was performed in October 2016. We also searched trial registries in November 2017 to identify potentially eligible trials. Bibliographies of retrieved articles were checked for additional references. No language restriction was applied (Supplemental Digital Content, Search Strategy, http://links.lww.com/AA/C359).

Study Selection

Studies were selected independently by 2 authors (C.T., M.Z.). One (C.T.) screened all references based on titles and abstracts and excluded references that obviously did not adhere to our inclusion criteria. Criteria for inclusion and noninclusion were checked by a further author (A.S.). Full reports were screened for final inclusion by 2 authors (C.T., A.S.).

Data-Collecting Process

One author (C.T.) extracted all relevant information from the original reports. Another author (A.S.) checked all extracted data. Discrepancies were resolved through discussion with an additional author (N.E.). Authors of included studies were contacted to obtain supplemental relevant information; for instance, we asked them for exact values of means and standard deviations (SDs) that were reported in graphs only, or for data reported as medians with ranges, or for unpublished outcomes. If contacting the authors was unsuccessful, we extracted the data from the graphs, and extrapolated means and SD from the published medians and ranges.[11]

Data Items

We extracted information on journal name, year of publication, first author's name, type of surgery and anesthetic procedures, number of randomized, excluded, and eventually analyzed patients, type and regimen of the LA, and regimen of epinephrine and of other adjuvants.

Predefined primary outcomes for the assessment of the impact of adding epinephrine to LAs were duration of analgesia, time to 2 segments regression (for intrathecal anesthesia), total consumption of LAs, and adverse effects. While going through the studies, we realized that some of our predefined outcomes were not relevant for all types of regional anesthesia. For instance, duration of analgesia is less an issue when analgesia is performed with an epidural catheter since reinjection of the anesthetic drug is possible. To focus on clinically relevant outcomes, we redefined outcomes of primary interest according to anesthesia techniques and settings (Table 1). For instance, we assumed that the adjunction of epinephrine to epidural LAs was useful only if it decreased the incidence of arterial hypotension or urinary retention or if it prolonged the duration of postoperative analgesia. Similarly, we assumed that the adjunction of epinephrine to LAs for a plexus block was useful only if it prolonged analgesia without prolonging motor block. All other outcomes that were reported in the original studies were extracted and considered as secondary outcomes.

Risk of Bias in Individual Studies

We assessed the quality of individual trials using the Cochrane risk of bias tool which contains 6 items rated as

Table 1. Modified Outcomes of Primary Interest

Route of Administration	Outcomes of Interest	Settings
Epidural	Motor block	Labor, postoperative analgesia
	Arterial hypotension	Labor, surgical anesthesia, postoperative analgesia
	Urinary retention	Labor, postoperative analgesia
	VAS pain at rest	Labor, postoperative analgesia
Intrathecal	Arterial hypotension	Labor CSE, surgical anesthesia
	Duration of analgesia	Surgical anesthesia
	Duration of motor block	Surgical anesthesia
	Time to 2 segments regression	Surgical anesthesia
	Motor block	Labor CSE
	Urinary retention	Labor CSE
Locoregional anesthesia	Duration of motor block	Surgical anesthesia
	Duration of analgesia	Surgical anesthesia
	Time to reach adequate block	Surgical anesthesia

Abbreviations: CSE, combined spinal-epidural anesthesia; VAS, visual analog scale.

low, high, or unclear risk of bias.[12] Because small trials tend to overestimate treatment effects, study size was included under the criterion "other bias." For the purpose of this analysis, we arbitrarily defined a study size <50 patients as a high risk of bias. Quality assessment was done by 1 author (C.T.) and checked by another author (A.S.). Discrepancies were discussed with a third author (N.E.).

Statistical Analyses

All analyses were stratified according to the 3 routes of epinephrine administration (epidural, intrathecal, locoregional), and subgroups were computed within each stratum according to the different clinical settings (labor, perioperative, postoperative) to provide information that is clinically relevant.

There was an arbitrary pre hoc decision to analyze data only when they were reported in at least 3 studies or 100 patients. For continuous outcomes, we extracted means and SDs for experimental and control groups, as reported in the original trials. Mean differences with 95% CIs were then computed for each study separately and a pooled estimate of mean differences was computed as a weighted mean difference (WMD) using the inverse variance method for the calculation of the weights of the different studies. For binary outcomes, we extracted the cumulative number of events reported in the experimental and control groups separately and computed an estimation of the effect of the intervention on the outcome using relative risks (RRs) and 95% CIs. The Mantel-Haenszel method was then used to pool all the RRs across studies. There was a pre hoc decision to use a random-effects model for all analyses because the impact of adding epinephrine to an LA may differ according to different study settings. In case of statistical evidence of heterogeneity (P value for the test of heterogeneity <.1), we intended to perform sensitivity analyses to search for the sources of heterogeneity.

For studies that compared different doses of epinephrine added to a single LA regimen, we checked whether the different doses resulted in statistically significant differences in outcomes. When the data were homogeneous (P value for the test of heterogeneity >.1), we pooled them. If not ($P < .1$), we selected the dose that was closest to the doses examined in the other trials.

We adapted the α levels of our analyses to account for multiple outcome testing within each of the 3 routes of epinephrine administration (epidural, intrathecal, locoregional), taking into account the subgroup analyses performed for the different clinical settings (labor, perioperative, postoperative) based on the pragmatic recommendations by Jakobsen et al,[13] which suggest dividing the standard 0.05 with the value situated halfway between 1 (no adjustment) and the number of primary outcomes compared (Bonferroni adjustment). For all primary outcomes, related to the epidural administration of epinephrine, this resulted in an α level of .01 and a 99% CI around the pooled point estimates (4 outcomes, 9 subgroups ($0.05/[\{9 + 1\}/2]) = 0.01$) instead of the conventional 0.05 and 95% CI. Similarly, the α level was set at .01 for all primary outcomes related to the intrathecal administration of epinephrine (6 outcomes, 7 subgroup analyses), and at .02 for those related to intrablock administration of epinephrine (3 outcomes, no subgroup analyses). For secondary outcomes, all α levels were set at .01.

Meta-analyses were performed using RevMan version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), STATA 15 (StataCorp, College Station, TX), and Microsoft Excel version 12.3.6 for Mac (Microsoft, Redmond, WA). For all outcomes of primary interest, we used funnel plots to visually assess the risk of publication bias. We additionally performed TSA (Trial Sequential Analysis, version 0.9.5.5 beta; Copenhagen Trial Unit, Copenhagen, Denmark, 2016), to add information regarding the number of patients required to reach a definite conclusion, considering a power of 80%, an α level of 1% (or 2% for locoregional anesthesia), and a 2-sided test.[14] For all TSA analyses, we assumed that adding epinephrine to an LA would be considered clinically relevant if it changed the outcome by 30%–50% depending on the end point. Details of assumptions tested are provided in Supplemental Digital Content, Table A, http://links.lww.com/AA/C359.

RESULTS

Selection of Trials

We retrieved 183 potentially relevant trial reports of which 70 underwent further analyses (Figure).[15–83]

Trial Characteristics

The 70 trials were published between 1970 and 2017 and included data on 3644 patients (Supplemental Digital Content, Table B, http://links.lww.com/AA/C359). They originated from 17 countries: United States (28 trials); United Kingdom (8); France (5); Belgium and Japan (4 each); Turkey and Finland (3 each); China, India, Korea, the Netherlands, and Sweden (2 each); and Canada, Ireland, Republic of Macedonia, Switzerland, and Taiwan (1 each). All reports were published in English except 2 that were published in French.[57,67] Median number of patients per trial was 44 (range, 9–174).

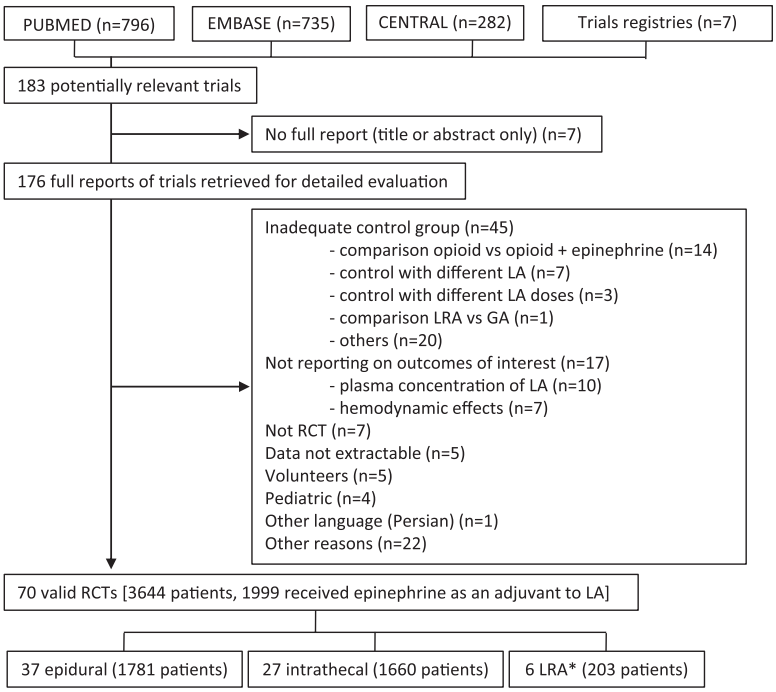

Figure. Flowchart. GA indicates general anesthesia; LA, local anesthetic; LRA, locoregional anesthesia (*axillary, popliteal, femoral, sciatic); RCT, randomized controlled trial.

In 37 trials (1781 patients), epinephrine was added to epidural LAs. In 12 of those, regimens were administered continuously through a catheter. In 27 trials (1660 patients), epinephrine was added to intrathecal LAs; of those, 8 were using a combined spinal-epidural (CSE) technique. Finally, in 6 trials (203 patients), epinephrine was added to an LA for locoregional anesthesia (sciatic, femoral, popliteal, axillary).

LAs used were bupivacaine (40 trials), lidocaine (10), ropivacaine (9), tetracaine (6), chloroprocaine (3), levobupivacaine (2), and lidocaine CO_2 or mepivacaine (1 trial each; numbers do not add up because 2 trials were using 2 different LAs). Further adjuvants were used in 29 trials and included fentanyl (18 trials), sufentanil (6), morphine (3), and butorphanol or clonidine (1 trial each).

Studies were performed in a variety of settings: labor (24 trials), cesarean delivery (15), orthopedic (13), urologic (6), general (4), gynecologic (3), lumbar spine (2), or vascular surgery (1). In 2 trials, patients underwent a variety of surgical interventions.[47,79] In 4 trials, general anesthesia was systematically administrated in combination with regional anesthesia,[69,72,76,80] and in 5 trials, general anesthesia was used as a rescue in case of failed regional anesthesia.[20,22,25,35,58]

Definitions of the end points varied among original studies. We used the definitions as reported in the trials (Supplemental Digital Content, Table C, http://links.lww.com/AA/C359).

Risks of biases are shown for each trial in Supplemental Digital Content, Figure A, http://links.lww.com/AA/C359.

We contacted the authors of 41 articles and asked for additional data; the authors of 14 articles responded and additional unpublished data from 3 trials could eventually be added to our analyses.[39,40,71]

Epidural Epinephrine

We found no evidence that adding epinephrine to an epidural LA changed any of the primary outcomes. Sample sizes were either too small to reach a definite conclusion (motor block, urinary retention) or sufficient to conclude on the futility of this adjunction (hypotension, pain intensity; Table 2, Supplemental Digital Content, Table A and Figures B1–B4, http://links.lww.com/AA/C359). Similarly, we found no evidence of an impact of epinephrine administration on any of the secondary outcomes (Table 3).

The impact of epidural epinephrine according to the different clinical settings is described in the following 3 paragraphs.

Labor Analgesia. Seventeen trials (886 patients) tested epinephrine added to epidural LAs for labor analgesia. Regimens were administrated as boluses in 11 trials,[15–18,36,37,44,45,56,73,82] and via a continuous infusion in 6 trials.[32,33,52,54,62,64] LAs were bupivacaine (13 trials), and chloroprocaine, levobupivacaine, lidocaine, or ropivacaine (1 trial each). Concentrations of epinephrine ranged from 1 to 5 $\mu g \cdot mL^{-1}$. The required sample sizes were not reached to definitely conclude on the impact of epinephrine on the duration of motor block: information size (IS) (4%), arterial hypotension (20%), urinary retention (23%), or pain intensity at rest (27%). There were too few trials to assess graphical evidence of publication bias (Table 2, Supplemental Digital Content, Table A and Figures B1-2, B2-2, B3-1, and B4-2, http://links.lww.com/AA/C359). We found no evidence of an impact of epinephrine on the incidences of ephedrine requirement, postoperative nausea and vomiting (PONV), pruritus, sedation, Apgar <7 at 1 minute, umbilical arterial pH, the need for cesarean delivery, or for instrumentation for delivery (Table 3).

Surgical Anesthesia. Fifteen trials (605 patients) tested epinephrine added to epidural LAs for surgical anesthesia. Regimens were administrated as boluses in 14 trials,[21,23,26,34,38,49,50,53,58,61,65,72,79,81] and via a continuous infusion

Table 2. Outcomes of Primary Interest for Epidural, Intrathecal, and Locoregional Anesthesia

			Intervention		Control			99% CI						
	Comparisons (n)	Patients (n)	n	Tot	n	Tot	RR (WMD)	Low	High	*P*1	*P*2	*P*3	TSA Conclusion	References
Epidural														
Hypotension														
All	18	703	94	362	98	341	0.93	0.64	1.37	.65	.06	.37	Futile	
Labor	7	305	20	154	29	151	0.70	0.20	2.45	.46	.05		Unclear	15, 16, 18, 37, 45, 82
Surgical	10	321	70	168	68	153	0.98	0.69	1.39	.88	.21		Futile	23, 26, 38, 50, 53, 58, 61, 65, 79
Postoperative	1	77	4	40	1	37	3.7	0.22	62.03	.23	.23		Not performed	69
Motor block														
All	7	392	66	207	47	185	1.01	0.66	1.55	.95	.28	.13	Unclear	
Labor	4	210	53	116	27	94	1.29	0.53	3.14	.47	.08		Unclear	15, 36, 45, 56
Postoperative	3	182	13	91	20	91	0.66	0.33	1.35	.14	.87		Unclear	39, 40, 69
Urinary retention														
All	4	205	33	104	32	101	0.97	0.60	1.57	.88	.57		Unclear	
Labor	4	205	33	104	32	101	0.97	0.60	1.57	.88	.57		Unclear	33, 45, 79
Postoperative	No data													
VAS pain														
All	7	358	178		180		(−0.48)	−1.17	0.20	.07	.0006	.33	Futile	
Labor	3	155	78		77		(−0.84)	−2.26	0.59	.13	.0002		Unclear	32, 54, 73
Postoperative	4	203	100		103		(−0.21)	−1.07	0.65	.53	.11		Futile	29, 30, 39, 40
Intrathecal		0												
Hypotension														
All	11	720	98	441	56	279	1.04	0.68	1.59	.82	.71	.20	Unclear	
Labor (CSE)	5	333	30	198	10	135	1.78	0.48	6.66	.26	.24		Unclear	24, 41, 46, 63, 78
Surgical	6	495	68	243	46	144	0.9	0.62	1.29	.77	.71		Unclear	20, 48, 67, 68, 84
Duration of analgesia														
Surgical	8	482	268		214		(33.76)	5.91	61.61	.002	.0003		Effective	43, 48, 55, 60, 68
Duration of motor block														
Surgical	14	634	348		286		(63.99)	36.59	91.39	<.00001	<.0001		Effective	19, 20, 22, 27, 28, 31, 43, 55, 60, 66, 67, 83
Time to 2 segments regression														
Surgical	12	504	300		204		(19.60)	11.18	28.03	<.00001	.07		Effective	19, 20, 22, 25, 27, 51, 55, 66, 67, 83
Motor block														
Surgical (CSE)	4	290	177		113		1.66	0.69	3.98	.14	.27		Unclear	42, 46, 63, 78
Urinary retention														
Surgical (CSE)	No data													
Locoregional anesthesia														
Duration of motor block														
Surgical	Not enough data													
Duration of analgesia[a]														
Surgical	7	203	102		101		(65.9)	31.59	100.2	<.00001	.08		Effective	35, 57, 70, 71, 74, 80
Time to reach adequate block														
Surgical	No data													

Abbreviations: CI, confidence interval; CSE, combined spinal-epidural; n, number of events; *P*1, *P* value of the overall effect; *P*2, *P* value of heterogeneity of the data; *P*3, *P* value of heterogeneity between clinical settings; RR, relative risk; tot, total number of patients per group; TSA, trial sequential analyses; WMD, weighted mean difference.

[a]98% CIs are provided instead of 99% CIs.

Table 3. Other Outcomes

	Comparisons (n)	Patients (n)	Intervention		Control		RR	99% CI		P1	P2	P3	References
			n	Tot	n	Tot	(WMD)	Low	High				
Epidural													
Ephedrine requirement													
All	14	705	69	368	75	337	0.95	0.67	1.34	.68	.37	.81	
Labor	3	262	7	133	9	129	0.81	0.17	3.96	.74	.27		33, 44, 73
Surgical	11	443	62	235	66	208	0.94	0.65	1.36	.69	.33		26, 34, 39, 49, 50, 53, 58, 61, 72, 81
PONV													
All	20	857	67	421	76	436	0.92	0.64	1.34	.59	.76	.48	
Labor	8	338	40	168	35	170	1.09	0.62	1.91	.70	.36		15, 32, 45, 54, 56, 73, 82
Surgical	7	231	16	110	27	121	0.74	0.37	1.49	.27	.74		26, 38, 61, 76, 79, 81
Postoperative	5	288	11	143	14	145	0.77	0.31	1.87	.45	.83		29, 30, 39, 40, 69
Pruritus													
All	9	515	126	257	125	258	0.98	0.81	1.2	.83	.39	.14	
Labor	5	290	75	145	66	145	1.10	0.83	1.46	.39	.36		32, 33, 54, 56, 73
Postoperative	4	225	51	112	59	113	0.88	0.67	1.15	.20	.62		29, 30, 40, 69
Sedation													
All	7	330	47	163	60	167	0.84	0.62	1.13	.13	.92	.88	
Labor	3	120	8	60	11	60	0.79	0.29	2.14	.55	.71		32, 82
Postoperative	4	210	39	103	49	107	0.84	0.62	1.15	.16	.75		29, 30, 39, 40
Apgar <7 at 1 min													
Labor	4	149	9	73	6	76	1.52	0.42	5.49	.40	.85		15, 17, 45, 54
Umbilical arterial pH													
All	14	376		204		172	(0.00)	−0.01	0.02	.56	.04	.76	
Labor	9	240		127		113	(0.00)	−0.02	0.03	.79	.02		15–18, 23, 38, 58, 62, 64
Surgical	5	136		77		59	(0.01)	−0.02	0.03	.42	.37		21, 23, 38, 53, 58
Bradycardia													
Surgical	4	132	9	66	7	66	1.18	0.35	3.93	.73	.67		26, 38, 65
Need for cesarean delivery													
Labor	14	721	64	373	65	348	0.94	0.63	1.41	.70	.94		15–18, 32, 33, 36, 37, 44, 54, 64, 73, 82
Need for instrumentation													
Labor	15	624	73	324	54	300	1.13	0.76	1.69	.42	.82		15, 16, 18, 32, 33, 36, 45, 52, 54, 56, 64, 73, 82
Intrathecal													
Ephedrine requirement													
All	9	541	91	325	51	216	1.01	0.71	1.42	.96	.92	.78	
Surgical	7	389	88	248	50	141	1.00	0.71	1.42	1.00	.99		47, 55, 66, 67, 83
Labor (CSE)	2	152	3	77	1	75	1.54	0.03	88.81	.78	.15		63, 78
Bradycardia													
Surgical	3	240	14	147	8	93	1.58	0.59	4.26	.23	.42	na	
PONV													
All	12	696	98	395	68	301	1.06	0.67	1.67	.74	.15	.04	
Labor (CSE)	5	327	39	195	13	132	2.12	0.78	5.81	.05	.3		24, 41, 42, 46, 63
Surgical	7	369	59	200	55	169	0.90	0.61	1.31	.45	.4		19, 20, 28, 43, 47, 77, 84
Pruritus													
All	12	595	146	334	110	261	1.07	0.82	1.41	.49	.2	0.65	
Labor (CSE)	6	372	120	218	83	154	1.08	0.88	1.31	.33	.56		24, 41, 42, 46, 63, 78
Surgical	6	223	26	116	27	107	0.88	0.29	2.69	.77	.05		19, 43, 55, 77, 85

(*Continued*)

Table 3. Continued

	Comparisons (n)	Patients (n)	Intervention		Control		RR (WMD)	99% CI		P1	P2	P3	References
			n	Tot	n	Tot		Low	High				
Time to reach highest sensory block													
Surgical	15	811		462		349	(1.39)	−0.15	2.93	.02	<.00001		22, 47, 48, 51, 55, 59, 60, 66–68, 83
VAS pain intensity at rest													
Surgical	5	253		126		127	(−0.20)	−0.48	0.08	.07	.02		24, 41, 43, 46, 63
Fetal bradycardia													
Labor (CSE)	4	229	16	117	18	112	0.84	0.37	1.89	.58	.99		24, 42, 63, 78
Need for cesarean delivery													
Labor (CSE)	4	221	14	143	7	78	1.35	0.42	4.33	.50	.97		24, 42, 46, 78
Need for instrumentation													
Labor (CSE)	5	332	30	198	38	134	0.71	0.42	1.23	.11	.84		41, 42, 46, 63, 78
Locoregional anesthesia													
Need for supplemental analgesia													
Surgical	4		9	62	11	57	0.70	0.25	2	.38	.71		35, 70, 71, 80

Abbreviations: CI, confidence interval; CSE, combined spinal-epidural; n, number of events; *P1*, *P* value of the overall effect; *P2*, *P* value of heterogeneity of the data; *P3*, *P* value of heterogeneity between clinical settings; PONV, postoperative nausea and vomiting; RR, relative risk; tot, total number of patients per group; WMD, weighted mean difference.

in 1 trial.[76] LAs were bupivacaine (9 trials), lidocaine or ropivacaine (2 each), and chloroprocaine or levobupivacaine (1 each). Concentrations of epinephrine ranged from 2.5 to 5 μg·mL^{-1}. The addition of epinephrine to epidural LAs showed no impact on the risk of intraoperative arterial hypotension. Although IS was not reached (50%), the limits of futility were crossed suggesting that further trials were unlikely to demonstrate a change of 20% on this outcome (Table 2, Supplemental Digital Content, Table A and Figures B2-3, http://links.lww.com/AA/C359). There was no evidence either that epidural epinephrine had an impact on the risks of ephedrine requirement, bradycardia, or PONV, or on umbilical arterial pH (Table 3).

Postoperative Analgesia. Five trials (290 patients) tested epinephrine added to a postoperative infusion of epidural LAs. Among them, 3 used a fixed infusion rate[39,40,69] and 2 used a fixed infusion rate in addition to patient-controlled epidural analgesia.[29,30] LAs were bupivacaine (3 trials) and ropivacaine (2 trials). Concentrations of epinephrine ranged from 0.5 to 5 μg·mL^{-1}. There was insufficient evidence to definitely conclude on the impact of epinephrine on motor block (IS, 31%). There were too few trials to test for publication bias. There was sufficient evidence to conclude that epinephrine did not decrease pain intensity at rest by >30% (Table 2, Supplemental Digital Content, Table A and Figures B4-3, http://links.lww.com/AA/C359). Incidences of PONV, pruritus, and sedation were not impacted by epinephrine (Table 3).

Intrathecal Epinephrine

We found evidence that adding epinephrine to an intrathecal LA significantly prolonged the duration of analgesia, motor block, and time to 2 segments regression. Its impact on the risk of hypotension and on the proportion of motor block when administrated in a CSE regimen remained unclear due to insufficient sample size (Table 2, Supplemental Digital Content, Table A and Figures B5–B9, http://links.lww.com/AA/C359). Similarly, we found no evidence of any impact of epinephrine on any of the secondary outcomes (Table 3). The impact of intrathecal epinephrine, according to the different clinical settings, is described in the following 2 paragraphs.

Surgical Anesthesia. Twenty-one studies (1289 patients) examined the effect of epinephrine added to intrathecal LAs for surgical procedures.[19,20,22,25,27,28,31,43,47,48,51,55,59,60,66–68,75,77,83,84] Two of those were using a CSE technique.[48,68] From these trials, we extracted the end points duration of analgesia and time to highest sensory block before the first epidural injection. LAs were bupivacaine (9 trials), tetracaine and lidocaine (5 each), and chloroprocaine (1). In 1 trial, both bupivacaine and tetracaine were tested.[60] Doses of epinephrine ranged from 15 to 500 μg. Intrathecal epinephrine significantly increased the duration of analgesia (WMD 34 minutes [99% CI, 5.9–62]; $P = .002$), the duration of motor block (64 minutes [37–91]; $P > .001$), and the time to 2 segments regression (20 minutes [11–28]; $P < .001$). The IS required was reached for the time to 2 segments regression. Although it was not reached for duration of analgesia and of motor block, the limits of the α spending boundaries

were crossed (Table 2, Supplemental Digital Content, Table A and Figures B6–B8, http://links.lww.com/AA/C359). The impact of intrathecal epinephrine on the incidence of hypotension remained unclear due to insufficient sample size (Table 2, Supplemental Digital Content, Table A and Figure B5-2, http://links.lww.com/AA/C359).

In addition, the incidences of bradycardia, ephedrine requirement, PONV, and pruritus; the time to reach the highest sensory block; and pain intensity at rest were analyzed. Intrathecal epinephrine increased the time to reach the highest sensory block (1.4 minutes [99% CI, 0.2–2.9]; $P < .001$). There was no evidence of an impact of adding epinephrine on the other end points (Table 3).

Combined Spinal-Epidural for Labor Analgesia. Six trials (371 patients) tested epinephrine added to intrathecal LAs for labor analgesia using the CSE technique.[24,41,42,46,63,78] LAs were bupivacaine (5 trials) and ropivacaine (1). Doses of epinephrine ranged from 2.25 to 200 µg. There were not enough data to definitely conclude on the impact of epinephrine on motor block (IS, 11%) or on arterial hypotension (11%) (Table 2, Supplemental Digital Content, Table A and Figures B5-3 and B9, http://links.lww.com/AA/C359). Incidences of ephedrine requirement, PONV, pruritus, need for cesarean delivery or instrumentation, or the risk of neonatal bradycardia were not impacted by epinephrine (Table 3).

Locoregional Anesthesia

Six trials (203 patients) tested epinephrine added to an LA for locoregional anesthesia.[35,57,70,71,74,80] LAs used were ropivacaine (3 trials), lidocaine (1), and mepivacaine (1). One trial tested both lidocaine and lidocaine CO_2.[57] Doses of epinephrine ranged from 100 to 300 µg. Epinephrine increased the duration of analgesia (WMD 66 minutes [98% CI, 32–100]); the required IS was reached (Table 2, Supplemental Digital Content, Table A and Figure B10, http://links.lww.com/AA/C359). Incidence of block failure was reported in 4 trials; we found no evidence that it was influenced by epinephrine (Table 3).[35,70,71,80] Two studies reported on the duration of motor block; they both suggested that epinephrine prolonged the motor block, but there were not enough patients to allow for data computation.[35,74]

Sensitivity Analyses

Significant heterogeneity was found for some of the primary outcomes.

Epidural for Labor Analgesia. The degree of heterogeneity could be decreased for the outcome arterial hypotension by regrouping the trials using bupivacaine (P for heterogeneity = .12); this did not change our estimate significantly (RR of this subgroup changed from 0.70 [99% CI, 0.27–1.81] to 0.51 [0.19–1.37]).

Intrathecal Anesthesia for Surgery. The degree of heterogeneity could be decreased by regrouping trials according to the LA used for the outcome duration of analgesia. This did not change our estimates.

For all other primary outcomes, the number of trials or patients per stratum were insufficient to perform sensitivity analyses.

DISCUSSION

Summary of Findings

We assessed the impact of adding epinephrine to an LA for regional anesthesia. We were able to conclude that adding epinephrine to epidural LAs did not decrease postoperative pain intensity by at least 30%, and did not impact the risk of intraoperative arterial hypotension. Also, adding epinephrine to intrathecal LAs increased the duration of motor block by about 60 minutes, of analgesia by about 30 minutes, and the time to 2 segments regression by 20 minutes. Adding epinephrine to LAs for a locoregional block significantly increased the duration of analgesia by about 60 minutes. Other important results of this systematic review were to identify the knowledge gaps. The IS, thus the number of patients needed to reach a definite conclusion, was insufficient to conclude on the impact of epinephrine on a variety of end points, for instance, on motor block when administrated through an epidural catheter, or on the risk of arterial hypotension when administrated intrathecally.

What Is Already Known on This Subject?

The role of epinephrine adjunction has been addressed in 2 systematic reviews.[8,9] One, examining the impact of adding epinephrine to epidural LAs in 7 trials (257 patients),[8] was inconclusive due to the limited number of trials. The second, including 24 trials (1271 patients), addressed the role of epinephrine added to intrathecal LAs.[9] Similar to our findings, the authors concluded that intrathecal epinephrine prolonged the duration of analgesia and motor block as well as the time to 2 segments regression and to reach the highest sensory block. In contrast to our findings, they also found that intrathecal epinephrine increased the incidence of arterial hypotension and PONV, especially with doses ≤100 µg.

What Does This New Analysis Add?

Our systematic review included more trials than previously published ones.[8,9] We were able to investigate the impact of epinephrine added to LAs in various settings, such as labor, surgery, or postoperative analgesia. We included TSA to estimate the number of patients needed to reach definite conclusions on benefit and harm, and we adapted α levels to adjust for multiple outcomes testing. Interestingly, for most outcomes, the available IS was still too small to allow for reliable conclusions to be drawn. Finally, our analyses are the first to evaluate the adjunction of epinephrine to locoregional anesthesia.[86] When added to an LA used for a sciatic, femoral, popliteal, or axillary block, epinephrine is likely to increase the duration of postoperative analgesia by about 1 hour.

Weaknesses of Our Analysis

This systematic review has several limitations; most are due to weaknesses of the original studies. First, the majority of the trials included <50 patients, bearing the risk to report exaggerated beneficial effects.[87] Second, many outcomes were not standardized. This may be due to the lack of a common, clearly defined research agenda. Third, we combined outcomes that were not necessarily the primary outcomes in the included trials. Although this may have added heterogeneity to our analyses, it also increased their power and generalizability. Fourth, a large variety of LA regimens were used with

different vasoconstrictive properties which may influence their pharmacokinetics.[88] Fifth, although epinephrine doses varied across trials, we were unable to establish dose-responsiveness. Finally, although we have adapted the α levels of statistical significance to adjust for multiple testing, there is yet no consensus on which method of adjustment should be used, and some may not agree with our pragmatic method. Similarly, for the purpose of clarity, we have maintained the adjusted α levels to perform TSA. The number of missing patients to achieve definite conclusions may therefore be overestimated.

Clinical Implications

Epinephrine has been used for many years as an adjuvant to LAs with the aim to prolong sensory nerve blockade and delay systemic uptake of the LA, thereby reducing the risk of anesthetic toxicity. This systematic review suggests that the duration of analgesia is likely to be prolonged by about 30 minutes when epinephrine is added to intrathecal LAs and by about 60 minutes when added to locoregional LAs. This degree of efficacy must be put into its clinical context. Adding clonidine to intermediate or long-acting LAs for a single-shot peripheral nerve or plexus block prolongs duration of analgesia by about 120 minutes,[89] and to intrathecal LAs, by about 100 minutes.[90] Opioids added to LAs prolong the duration of postoperative analgesia even more, that is, by 120 minutes with the short-acting fentanyl, and by more than 8 hours with morphine.[91] Also, adding dexamethasone or dexmedetomidine to LAs was shown to prolong duration of analgesia by about 4 and 7 hours, respectively.[85,92] These data suggest that there are more powerful alternatives than epinephrine to prolong analgesia. The question remains, whether epinephrine as an adjuvant reduces the risk of systemic LA toxicity. However, unless the LA is injected in very high doses, for instance, through multiple subcutaneous infiltrations, the risk of systemic LA toxicity may be negligible.

Research Agenda

TSA suggested that further trials on epinephrine added to intrathecal LAs are probably not needed because its impact seems well characterized. However, in the context of labor analgesia, when epinephrine is added to an intrathecal or epidural LA, the available evidence is still not sufficient to conclude on its impact on motor block, on arterial hypotension, or on the need for instrumentation or cesarean delivery. Also, well-designed RCTs are necessary to better characterize the impact of epinephrine added to an LA in an epidural catheter for both labor and postoperative analgesia. Finally, dose-responsiveness and the adequate dose of epinephrine that needs to be administrated still need to be defined.

CONCLUSIONS

Adding epinephrine to intrathecal or locoregional LAs prolongs analgesia and motor block by 30–60 minutes. The impact of adding epinephrine to epidural LAs or to a CSE remains uncertain.

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REFERENCES

1. Bloom SL, Spong CY, Weiner SJ, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Complications of anesthesia for cesarean delivery. *Obstet Gynecol*. 2005;106:281–287.
2. Hadzic A, Arliss J, Kerimoglu B, et al. A comparison of infraclavicular nerve block versus general anesthesia for hand and wrist day-case surgeries. *Anesthesiology*. 2004;101:127–132.
3. Leighton BL, Halpern SH. The effects of epidural analgesia on labor, maternal, and neonatal outcomes: a systematic review. *Am J Obstet Gynecol*. 2002;186:S69–S77.
4. Tyritzis SI, Stravodimos KG, Vasileiou I, et al. Spinal versus general anaesthesia in postoperative pain management during transurethral procedures. *ISRN Urol*. 2011;2011:895874.
5. Bernards CM, Kopacz DJ. Effect of epinephrine on lidocaine clearance in vivo: a microdialysis study in humans. *Anesthesiology*. 1999;91:962–968.
6. Lee BB, Ngan Kee WD, Plummer JL, Karmakar MK, Wong AS. The effect of the addition of epinephrine on early systemic absorption of epidural ropivacaine in humans. *Anesth Analg*. 2002;95:1402–7, .
7. Sonohata M, Furue H, Katafuchi T, et al. Actions of noradrenaline on substantia gelatinosa neurones in the rat spinal cord revealed by in vivo patch recording. *J Physiol*. 2004;555:515–526.
8. Curatolo M, Petersen-Felix S, Scaramozzino P, Zbinden AM. Epidural fentanyl, adrenaline and clonidine as adjuvants to

local anaesthetics for surgical analgesia: meta-analyses of analgesia and side-effects. *Acta Anaesthesiol Scand*. 1998;42:910–920.
9. de Oliveira GS Jr, Balliu B, Nader A, McCarthy RJ. Dose-ranging effects of intrathecal epinephrine on anesthesia/analgesia: a meta-analysis and metaregression of randomized controlled trials. *Reg Anesth Pain Med*. 2012;37:423–432.
10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
11. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
12. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
13. Jakobsen JC, Wetterslev J, Lange T, Gluud C. Viewpoint: taking into account risks of random errors when analysing multiple outcomes in systematic reviews. *Cochrane Database Syst Rev*. 2016;3:ED000111.
14. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. *User Manual for Trial Sequential Analysis (TSA)*. Copenhagen, Denmark: Denmark Copenhagen Trial Unit, Cent. Clin. Interv. Res, 2011. Available at: www.ctu.dk/tsa. Accessed November 21, 2017.
15. Abboud TK, Afrasiabi A, Zhu J, et al. Bupivacaine/butorphanol/epinephrine for epidural anesthesia in obstetrics: maternal and neonatal effects. *Reg Anesth*. 1989;14:219–224.
16. Abboud TK, David S, Nagappala S, et al. Maternal, fetal, and neonatal effects of lidocaine with and without epinephrine for epidural anesthesia in obstetrics. *Anesth Analg*. 1984;63:973–979.
17. Abboud TK, DerSarkissian L, Terrasi J, Murakawa K, Zhu J, Longhitano M. Comparative maternal, fetal, and neonatal effects of chloroprocaine with and without epinephrine for epidural anesthesia in obstetrics. *Anesth Analg*. 1987;66:71–75.
18. Abboud TK, Sheik-ol-Eslam A, Yanagi T, et al. Safety and efficacy of epinephrine added to bupivacaine for lumbar epidural analgesia in obstetrics. *Anesth Analg*. 1985;64:585–591.
19. Abouleish E, Rawal N, Tobon-Randall B, et al. A clinical and laboratory study to compare the addition of 0.2 mg of morphine, 0.2 mg of epinephrine, or their combination to hyperbaric bupivacaine for spinal anesthesia in cesarean section. *Anesth Analg*. 1993;77:457–462.
20. Abouleish EI. Epinephrine improves the quality of spinal hyperbaric bupivacaine for cesarean section. *Anesth Analg*. 1987;66:395–400.
21. Alahuhta S, Räsänen J, Jouppila P, Jouppila R, Hollmén AI. Uteroplacental and fetal circulation during extradural bupivacaine-adrenaline and bupivacaine for caesarean section in hypertensive pregnancies with chronic fetal asphyxia. *Br J Anaesth*. 1993;71:348–353.
22. Armstrong IR, Littlewood DG, Chambers WA. Spinal anesthesia with tetracaine–effect of added vasoconstrictors. *Anesth Analg*. 1983;62:793–795.
23. Brose WG, Cohen SE. Epidural lidocaine for cesarean section: effect of varying epinephrine concentration. *Anesthesiology*. 1988;69:936–940.
24. Campbell DC, Banner R, Crone LA, Gore-Hickman W, Yip RW. Addition of epinephrine to intrathecal bupivacaine and sufentanil for ambulatory labor analgesia. *Anesthesiology*. 1997;86:525–531.
25. Carpenter RL, Smith HS, Bridenbaugh LD. Epinephrine increases the effectiveness of tetracaine spinal anesthesia. *Anesthesiology*. 1989;71:33–36.
26. Cederholm I, Anskär S, Bengtsson M. Sensory, motor, and sympathetic block during epidural analgesia with 0.5% and 0.75% ropivacaine with and without epinephrine. *Reg Anesth*. 1994;19:18–33.
27. Chambers WA, Littlewood DG, Scott DB. Spinal anesthesia with hyperbaric bupivacaine: effect of added vasoconstrictors. *Anesth Analg*. 1982;61:49–52.
28. Chen TY, Tseng CC, Wang LK, Tsai TY, Chen BS, Chang CL. The clinical use of small-dose tetracaine spinal anesthesia for transurethral prostatectomy. *Anesth Analg*. 2001;92:1020–1023.
29. Cohen S, Amar D, Pantuck CB, et al. Epidural patient-controlled analgesia after cesarean section: buprenorphine-0.015% bupivacaine with epinephrine versus fentanyl-0.015% bupivacaine with and without epinephrine. *Anesth Analg*. 1992;74:226–230.
30. Cohen S, Lowenwirt I, Pantuck CB, Amar D, Pantuck EJ. Bupivacaine 0.01% and/or epinephrine 0.5 microg/ml improve epidural fentanyl analgesia after cesarean section. *Anesthesiology*. 1998;89:1354–1361.
31. Concepcion M, Maddi R, Francis D, Rocco AG, Murray E, Covino BG. Vasoconstrictors in spinal anesthesia with tetracaine–a comparison of epinephrine and phenylephrine. *Anesth Analg*. 1984;63:134–138.
32. Connelly NR, Freiman JP, Lucas T, et al. Addition of epinephrine to epidural bupivacaine infusions following initiation of labor analgesia with epidural fentanyl. *J Clin Anesth*. 2011;23:265–269.
33. Dahl V, Hagen I, Koss KS, Nordentoft J, Raeder JC. Bupivacaine 2.5 mg/ml versus bupivacaine 0.625 mg/ml and sufentanil 1 microg/ml with or without epinephrine 1 microg/ml for epidural analgesia in labour. *Int J Obstet Anesth*. 1999;8:155–160.
34. Darshan MS, Sri Devi S, Karthik A, Jeyakumar V, Karthik M, Nagasunitha CH. Epinephrine as epidural adjuvant to bupivacaine and fentanyl in elective orthopedic surgeries. *Sch J App Med Sci*. 2014;2:1540–1550.
35. Dogru K, Duygulu F, Yildiz K, Kotanoglu MS, Madenoglu H, Boyaci A. Hemodynamic and blockade effects of high/low epinephrine doses during axillary brachial plexus blockade with lidocaine 1.5%: a randomized, double-blinded study. *Reg Anesth Pain Med*. 2003;28:401–405.
36. Dounas M, O'Kelly BO, Jamali S, Mercier FJ, Benhamou D. Maternal and fetal effects of adrenaline with bupivacaine (0.25%) for epidural analgesia during labour. *Eur J Anaesthesiol*. 1996;13:594–598.
37. Eisenach JC, Grice SC, Dewan DM. Epinephrine enhances analgesia produced by epidural bupivacaine during labor. *Anesth Analg*. 1987;66:447–451.
38. Feng SW, Cao Y, Wang WG, Liu YS, Shen XF. Addition of adrenaline to chloroprocaine provides a moderate duration time for epidural anaesthesia in elective caesarean section. *J Int Med Res*. 2012;40:1099–1107.
39. Förster JG, Lumme HM, Palkama VJ, Rosenberg PH, Pitkänen MT. Epinephrine 4 microg/mL added to a low-dose mixture of ropivacaine and fentanyl for lumbar epidural analgesia after total knee arthroplasty. *Anesth Analg*. 2008;106:301–304.
40. Förster JG, Niemi TT, Aromaa U, Neuvonen PJ, Seppälä TA, Rosenberg PH. Epinephrine added to a lumbar epidural infusion of a small-dose ropivacaine-fentanyl mixture after arterial bypass surgery of the lower extremities. *Acta Anaesthesiol Scand*. 2003;47:1106–1113.
41. Gautier PE, Debry F, Fanard L, Van Steenberge A, Hody JL. Ambulatory combined spinal-epidural analgesia for labor. Influence of epinephrine on bupivacaine-sufentanil combination. *Reg Anesth*. 1997;22:143–149.
42. Goodman SR, Kim-Lo SH, Ciliberto CF, Ridley DM, Smiley RM. Epinephrine is not a useful addition to intrathecal fentanyl or fentanyl-bupivacaine for labor analgesia. *Reg Anesth Pain Med*. 2002;27:374–379.
43. Goyagi T, Nishikawa T. The addition of epinephrine enhances postoperative analgesia by intrathecal morphine. *Anesth Analg*. 1995;81:508–513.
44. Grice SC, Eisenach JC, Dewan DM. Labor analgesia with epidural bupivacaine plus fentanyl: enhancement with epinephrine and inhibition with 2-chloroprocaine. *Anesthesiology*. 1990;72:623–628.
45. Gupta S, Rathore P, Raiger LK. Epidural for labour analgesia–bupivacaine + fentanyl vs bupivacaine + fentanyl + epinephrine. *Middle East J Anaesthesiol*. 2005;18:611–622.
46. Gurbet A, Turker G, Kose DO, Uckunkaya N. Intrathecal epinephrine in combined spinal-epidural analgesia for labor: dose-response relationship for epinephrine added to a local anesthetic-opioid combination. *Int J Obstet Anesth*. 2005;14:121–125.
47. Inoue S, Kawaraguchi Y, Kitaguchi K, Furuya H. Inclusion of epinephrine to hyperbaric tetracaine and the supine position enhance the cephalad spread of spinal anaesthesia compared

with hyperbaric teracaine alone in the lithotomy position. *Acta Anaesthesiol Scand*. 2004;48:342–346.
48. Kim WH, Ko JS, Ahn HJ, et al. Epinephrine decreases the dose of hyperbaric bupivacaine necessary for tourniquet pain blockade during spinal anesthesia for total knee replacement arthroplasty. *J Anesth*. 2013;27:72–79.
49. Kopacz DJ, Helman JD, Nussbaum CE, Hsiang JN, Nora PC, Allen HW. A comparison of epidural levobupivacaine 0.5% with or without epinephrine for lumbar spine surgery. *Anesth Analg*. 2001;93:755–760.
50. Laishley RS, Morgan BM. A single dose epidural technique for caesarean section. A comparison between 0.5% bupivacaine plain and 0.5% bupivacaine with adrenaline. *Anaesthesia*. 1988;43:100–103.
51. Leicht CH, Carlson SA. Prolongation of lidocaine spinal anesthesia with epinephrine and phenylephrine. *Anesth Analg*. 1986;65:365–369.
52. Leonard SA, Flynn R, Kelleher N, Shorten GD. Addition of epinephrine to epidural ropivacaine during labour–effects on onset and duration of action, efficacy, and systemic absorption of ropivacaine. *Int J Obstet Anesth*. 2002;11:180–184.
53. Lindblad A, Bernow J, Vernersson E, Marsál K. Effects of extradural anaesthesia on human fetal blood flow in utero. Comparison of three local anaesthetic solutions. *Br J Anaesth*. 1987;59:1265–1272.
54. Lysak SZ, Eisenach JC, Dobson CE 2nd. Patient-controlled epidural analgesia during labor: a comparison of three solutions with a continuous infusion control. *Anesthesiology*. 1990;72:44–49.
55. Malinow AM, Mokriski BL, Nomura MK, et al. Effect of epinephrine on intrathecal fentanyl analgesia in patients undergoing postpartum tubal ligation. *Anesthesiology*. 1990;73:381–385.
56. Martin R, Lamarche Y, Tétrault JP, Tétrault L, Veilleux LJ. Effect of epinephrine addition to epidural morphine in obstetric analgesia. *Reg Anesth*. 1985;10:129–132.
57. Martin R, Martin G, Martin D, Vallet P, Jean M, Tétrault JP. [Effects of CO_2 and adrenaline on 1% lidocaine in axillary block]. *Ann Fr Anesth Reanim*. 1997;16:479–482.
58. McLintic AJ, Danskin FH, Reid JA, Thorburn J. Effect of adrenaline on extradural anaesthesia, plasma lignocaine concentrations and the feto-placental unit during elective caesarean section. *Br J Anaesth*. 1991;67:683–689.
59. Moore CH, Wilhite A, Pan PH, Blass NH. The addition of epinephrine to subarachnoid administered hyperbaric bupivacaine with fentanyl for cesarean delivery: the effect on onset time. *Reg Anesth*. 1992;17:202–204.
60. Moore DC. Spinal anesthesia: bupivacaine compared with tetracaine. *Anesth Analg*. 1980;59:743–750.
61. Noble DW, Morrison LM, Brockway MS, McClure JH. Adrenaline, fentanyl or adrenaline and fentanyl as adjuncts to bupivacaine for extradural anaesthesia in elective caesarean section. *Br J Anaesth*. 1991;66:645–650.
62. Okutomi T, Amano K, Morishima HO. Effect of standard diluted epinephrine infusion on epidural anesthesia in labor. *Reg Anesth Pain Med*. 2000;25:529–534.
63. Okutomi T, Mochizuki J, Amano K, Datta S. The effect of intrathecal epinephrine on epidural infused analgesics during labor. *Reg Anesth Pain Med*. 2003;28:108–112.
64. Okutomi T, Mochizuki J, Amano K, Hoka S. Effect of epidural epinephrine infusion with bupivacaine on labor pain and mother-fetus outcome in humans. *Reg Anesth Pain Med*. 2000;25:228–234.
65. Pither CE, Emanuelsson BM, Reventlid H, Whitehead E. A comparison of the dynamics and pharmacokinetics of ropivacaine 7.5 mg/mL with and without epinephrine used for epidural anaesthesia in urological surgery. *Clin Drug Investig*. 2003;23:245–253.
66. Racle JP, Benkhadra A, Poy JY, Gleizal B. Effect of increasing amounts of epinephrine during isobaric bupivacaine spinal anesthesia in elderly patients. *Anesth Analg*. 1987;66:882–886.
67. Racle JP, Poy JY, Benkhadra A, Jourdren L, Fockenier F. [Prolongation of spinal anesthesia with hyperbaric bupivacaine by adrenaline and clonidine in the elderly]. *Ann Fr Anesth Reanim*. 1988;7:139–144.
68. Randalls B, Broadway JW, Browne DA, Morgan BM. Comparison of four subarachnoid solutions in a needle-through-needle technique for elective caesarean section. *Br J Anaesth*. 1991;66:314–318.
69. Sakaguchi Y, Sakura S, Shinzawa M, Saito Y. Does adrenaline improve epidural bupivacaine and fentanyl analgesia after abdominal surgery? *Anaesth Intensive Care*. 2000;28:522–526.
70. Schoenmakers KP, Fenten MG, Louwerens JW, Scheffer GJ, Stienstra R. The effects of adding epinephrine to ropivacaine for popliteal nerve block on the duration of postoperative analgesia: a randomized controlled trial. *BMC Anesthesiol*. 2015;15:100.
71. Schoenmakers KP, Vree TB, Jack NT, van den Bemt B, van Limbeek J, Stienstra R. Pharmacokinetics of 450 mg ropivacaine with and without epinephrine for combined femoral and sciatic nerve block in lower extremity surgery. A pilot study. *Br J Clin Pharmacol*. 2012;75:1321–1327.
72. Senard M, Ledoux D, Darmon PL, Hans P, Brichant JF, Bonnet F. Hemodynamic effects of epinephrine associated to an epidural clonidine-bupivacaïne mixture during combined lumbar epidural and general anesthesia. *Acta Anaesthesiol Belg*. 1998;49:167–173.
73. Soetens FM, Soetens MA, Vercauteren MP. Levobupivacaine-sufentanil with or without epinephrine during epidural labor analgesia. *Anesth Analg*. 2006;103:182–186.
74. Song JH, Shim HY, Lee TJ, et al. Comparison of dexmedetomidine and epinephrine as an adjuvant to 1% mepivacaine in brachial plexus block. *Korean J Anesthesiol*. 2014;66:283–289.
75. Spivey DL. Epinephrine does not prolong lidocaine spinal anesthesia in term parturients. *Anesth Analg*. 1985;64:468–470.
76. Taleska G, Trajkovska T, Kokareva A, et al. Preemptive epidural analgesia with bupivacaine and sufentanyl and the effects of epiduraly added epinephrine for thoracic surgery. *Maced J Med Sci*. 2010;3:46–53.
77. Turker G, N UC, Yilmazlar A, Demirag B, Tokat O. Effects of adding epinephrine plus fentanyl to low-dose lidocaine for spinal anesthesia in outpatient knee arthroscopy. *Acta Anaesthesiol Scand*. 2003;47:986–992.
78. Vercauteren MP, Jacobs S, Jacquemyn Y, Adriaensen HA. Intrathecal labor analgesia with bupivacaine and sufentanil: the effect of adding 2.25 microg epinephrine. *Reg Anesth Pain Med*. 2001;26:473–477.
79. Waters HR, Rosen N, Perkins DH. Extradural blockade with bupivacaine. A double blind trial of bupivacaine with adrenaline 1-200,000, and bupivacaine plain. *Anaesthesia*. 1970;25:184–190.
80. Weber A, Fournier R, Van Gessel E, Riand N, Gamulin Z. Epinephrine does not prolong the analgesia of 20 mL ropivacaine 0.5% or 0.2% in a femoral three-in-one block. *Anesth Analg*. 2001;93:1327–1331.
81. Wilson CM, Moore J, Ghaly RG, Flynn R, McClean E, Dundee JW. Plasma concentrations of bupivacaine during extradural anaesthesia for caesarean section. The effect of adrenaline. *Anaesthesia*. 1988;43:12–15.
82. Yau G, Gregory MA, Gin T, Oh TE. Obstetric epidural analgesia with mixtures of bupivacaine, adrenaline and fentanyl. *Anaesthesia*. 1990;45:1020–1023.
83. Racle JP, Benkhadra A, Poy JY. Subarachnoid anaesthesia produced by hyperbaric lignocaine in elderly patients. Prolongation of effect with adrenaline. *Br J Anaesth*. 1988;60:831–835.
84. Katz D, Beilin Y. Does the addition of epinephrine prolong the duration of spinal anesthesia for repeat cesarean section? Prototol and results available on Clinicaltrials.gov (Identifier: NCT02369510). 2017.
85. Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. *Anaesthesia*. 2015;70:71–83.
86. Niemi G. Advantages and disadvantages of adrenaline in regional anaesthesia. *Best Pract Res Clin Anaesthesiol*. 2005;19:229–245.
87. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol*. 2000;53:1119–1129.
88. Lofstrom JB. 1991 Labat Lecture. The effect of local anesthetics on the peripheral vasculature. *Reg Anesth*. 1992;17:1–11.

89. Pöpping DM, Elia N, Marret E, Wenk M, Tramèr MR. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. *Anesthesiology*. 2009;111:406–415.
90. Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med*. 2008;33:159–167.
91. Pöpping DM, Elia N, Marret E, Wenk M, Tramèr MR. Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: a meta-analysis of randomized trials. *Pain*. 2012;153:784–793.
92. Vorobeichik L, Brull R, Abdallah FW. Evidence basis for using perineural dexmedetomidine to enhance the quality of brachial plexus nerve blocks: a systematic review and meta-analysis of randomized controlled trials. *Br J Anaesth*. 2017;118:167–181.